

**WHAT IS CLAIMED IS:**

1. A method for killing tumor vascular endothelial cells, comprising administering to an animal having a vascularized tumor a biologically effective amount of at least a first antibody, or antigen-binding region thereof, that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells.

10 2. A method for inducing coagulation in tumor vasculature, comprising administering to an animal having a vascularized tumor a vessel-occluding amount of at least a first antibody, or antigen-binding region thereof, that binds to an aminophospholipid on the luminal surface of tumor vasculature.

15 3. A method for destroying tumor vasculature, comprising administering to an animal having a vascularized tumor a tumor-destructive amount of at least a first antibody, or antigen-binding region thereof, that binds to an aminophospholipid on the luminal surface of tumor vasculature.

20 4. A method for treating an animal having a vascularized tumor, comprising administering to said animal a therapeutically effective amount of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor.

25 5. The method of claim 4, wherein said pharmaceutical composition comprises at least a first antibody, or antigen-binding fragment thereof, that binds to phosphatidylethanolamine on the luminal surface of blood vessels of the vascularized tumor.

30

6. The method of claim 4, wherein said pharmaceutical composition comprises at least a first antibody, or antigen-binding fragment thereof, that binds to phosphatidylserine on the luminal surface of blood vessels of the vascularized tumor.

5

7. The method of claim 4, wherein said pharmaceutical composition comprises at least a first IgG or IgM anti-aminophospholipid antibody.

10

8. The method of claim 4, wherein said pharmaceutical composition comprises at least a first scFv, Fv, Fab', Fab or F(ab')<sub>2</sub> antigen-binding fragment of an anti-aminophospholipid antibody.

15

9. The method of claim 4, wherein said pharmaceutical composition comprises at least a first human, humanized or part-human chimeric anti-aminophospholipid antibody or antigen-binding fragment thereof.

20

10. The method of claim 4, wherein said pharmaceutical composition comprises at least a first anti-aminophospholipid monoclonal antibody or antigen-binding fragment thereof.

25

11. The method of claim 10, wherein said pharmaceutical composition comprises at least a first anti-aminophospholipid monoclonal antibody, or antigen-binding fragment thereof, that is prepared by a preparative process comprising:

(a) preparing an anti-aminophospholipid antibody-producing cell; and

30

- (b) obtaining an anti-aminophospholipid monoclonal antibody from said antibody-producing cell.

5 12. The method of claim 11, wherein said anti-aminophospholipid antibody-producing cell is obtained from a human patient having a disease associated with the production of anti-aminophospholipid antibodies.

10 13. The method of claim 11, wherein said anti-aminophospholipid antibody-producing cell is obtained by stimulating a mixed population of human peripheral blood lymphocytes with an immunogenically effective amount of an aminophospholipid sample.

15 14. The method of claim 11, wherein said anti-aminophospholipid antibody-producing cell is obtained by immunizing an animal with an immunogenically effective amount of an aminophospholipid sample.

20 15. The method of claim 14, wherein said anti-aminophospholipid antibody-producing cell is obtained by immunizing a transgenic mouse that comprises a human antibody library with an immunogenically effective amount of an aminophospholipid sample.

25 16. The method of claim 11, wherein said preparative process comprises:

- (a) fusing said anti-aminophospholipid antibody-producing cell with an immortal cell to prepare a hybridoma that produces an anti-aminophospholipid monoclonal antibody; and

30

(b) obtaining an anti-aminophospholipid monoclonal antibody from said hybridoma.

17. The method of claim 11, wherein said preparative process comprises:

- 5
- (a) immunizing an animal with an immunogenically effective amount of an aminophospholipid sample;
- 10
- (b) preparing a collection of antibody-producing hybridomas from the immunized animal;
- (c) selecting from the collection a hybridoma that produces an anti-aminophospholipid antibody; and
- 15
- (d) culturing the selected hybridoma to provide the anti-aminophospholipid monoclonal antibody.

18. The method of claim 17, wherein an antigen-binding region of the anti-aminophospholipid monoclonal antibody is operatively attached to a human antibody framework or constant region.

19. The method of claim 17, wherein the immunized animal is a transgenic mouse that comprises a human antibody library and wherein the anti-aminophospholipid monoclonal antibody is a human monoclonal antibody.

20. The method of claim 11, wherein said preparative process comprises:

- (a) obtaining anti-aminophospholipid antibody-encoding nucleic acids from said anti-aminophospholipid antibody-producing cell; and
- (b) expressing said nucleic acids to obtain a recombinant anti-aminophospholipid monoclonal antibody.

21. The method of claim 11, wherein said preparative process comprises:

- (a) immunizing an animal with an immunogenically effective amount of an aminophospholipid sample;
- (b) preparing a combinatorial immunoglobulin phagemid library expressing RNA isolated from the spleen of the immunized animal;
- (c) selecting from the phagemid library a clone that expresses an anti-aminophospholipid antibody; and
- (d) expressing an anti-aminophospholipid antibody-encoding nucleic acid from said selected clone to provide a recombinant anti-aminophospholipid monoclonal antibody.

22. The method of claim 21, wherein the immunized animal is a transgenic mouse that comprises a human antibody library and wherein the recombinant anti-aminophospholipid monoclonal antibody is a recombinant human monoclonal antibody.

SUB  
A3

23. The method of claim 4, wherein said pharmaceutical composition comprises a dimer, trimer or multimer of an anti-aminophospholipid antibody or antigen-binding fragments thereof.

5 24. The method of claim 4, wherein at least a second antibody that binds to an aminophospholipid, or an antigen-binding fragment thereof, is administered to said animal.

SUB  
A4

10 25. The method of claim 4, wherein said pharmaceutical composition is administered to said animal via intravenous administration.

15 26. The method of claim 4, wherein an image of the vasculature of said vascularized tumor is first obtained by administering to said animal a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to and identifies an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor.

20 27. The method of claim 4, further comprising subjecting said animal to surgery or radiotherapy.

25 28. The method of claim 4, further comprising simultaneously or sequentially administering to said animal a therapeutically effective amount of at least a second anti-cancer agent.

30 29. The method of claim 28, wherein said at least a second anti-cancer agent is a chemotherapeutic, radiotherapeutic, anti-angiogenic or apoptosis-inducing agent.

30. The method of claim 28, wherein said at least a second anti-cancer agent is an antibody-therapeutic agent construct comprising a targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature; said targeting antibody or fragment thereof operatively  
5 linked to a therapeutic agent.

31. The method of claim 30, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a cell surface antigen of a tumor cell.

32. The method of claim 30, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a component of tumor stroma.

33. The method of claim 30, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of intratumoral blood vessels of a vascularized tumor.

34. The method of claim 33, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed component of intratumoral vasculature selected from the group consisting of an aminophospholipid, endoglin, a TGF $\beta$  receptor, E-selectin, P-selectin, VCAM-1, ICAM-1, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE,  $\alpha_v\beta_3$  integrin, pleiotropin, endosialin and an MHC Class II protein.

35. The method of claim 33, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-localized component of intratumoral vasculature selected from the group consisting of VEGF/VPF, FGF, TGF $\beta$ , a ligand that binds to a TIE, a tumor-associated

fibronectin isoform, scatter factor/hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF and TIMP.

5 36. The method of claim 30, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a cytotoxic agent.

10 37. The method of claim 36, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a plant-, fungus- or bacteria-derived toxin.

15 38. The method of claim 37, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to deglycosylated ricin A chain.

20 39. The method of claim 30, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a coagulation factor or to an antibody, or antigen-binding fragment thereof, that binds to a coagulation factor.

25 40. The method of claim 39, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to Tissue Factor, truncated Tissue Factor or a derivative thereof, or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor, truncated Tissue Factor or a derivative thereof.

30 41. The method of claim 4, wherein said animal is a human patient.



42. A method for treating cancer, comprising administering to an animal having a vascularized tumor a therapeutically effective amount of at least a first pharmaceutical composition comprising at least a first naked antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of intratumoral blood vessels of the vascularized tumor.

43. A method for treating cancer, comprising administering to an animal having a vascularized tumor at least a first pharmaceutical composition comprising an amount of at least a first unconjugated antibody effective to kill at least a portion of the tumor vascular endothelial cells; wherein said first unconjugated antibody is an unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid expressed on the luminal surface of tumor vascular endothelial cells.

44. A method for treating cancer, comprising administering to an animal having a vascularized tumor at least a first pharmaceutical composition comprising an amount of at least a first unconjugated antibody effective to occlude or destroy tumor blood vessels, as opposed to normal blood vessels; wherein said first unconjugated antibody is an unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid expressed on the luminal surface of tumor vascular endothelial cells.

45. A method for treating cancer, comprising administering to an animal having a vascularized tumor at least a first pharmaceutical composition comprising an amount of at least a first unconjugated antibody effective to induce tumor necrosis; wherein said first unconjugated antibody is an unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid expressed on the luminal surface of blood vessels of the vascularized tumor.

46. A method for treating cancer, comprising:

(a) forming an image of a vascularized tumor by administering to an animal having a vascularized tumor a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, thereby forming a detectable image of the tumor vasculature; and

(b) subsequently administering to said animal a therapeutically effective amount of at least a first antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the tumor blood vessel luminal surface and thereby destroys the tumor vasculature.

47. A method for treating cancer, comprising simultaneously or sequentially administering to an animal having a vascularized tumor a therapeutically effective combination of an unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor and at least a second anti-cancer agent.

48. The method of claim 47, wherein said at least a second anti-cancer agent is a chemotherapeutic, radiotherapeutic, anti-angiogenic or apoptosis-inducing agent or an antibody-therapeutic agent construct comprising a therapeutic agent operatively attached to an antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of tumor vasculature or tumor stroma.

ADD  
AS